REMARKS/ARGUMENTS

Claims 1-12 and 19-20 are active. Claims 13-18 have been withdrawn from consideration. The ranges in claims 1, 3 and 11 have been revised. Support for these amendments appears on page 7, lines 20-29. The Applicants do not believe that any new matter has been added. Favorable consideration of this amendment and allowance of the application is respectfully requested.

Restriction/Election

Applicants previously elected with traverse, Group I, Claims 1-12, directed to a pH-sensitive polymer and a method of making it. Claims 13-18, directed to medicinal substances containing the pH-sensitive polymer, have been withdrawn from consideration. The Restriction Requirement has now been made FINAL.

The Applicants respectfully request that the claims of the nonelected group which depend from or include all the limitations of those of elected Group I, be rejoined upon an indication of allowability for the elected claims, see MPEP 821.04.

Rejection—35 U.S.C. §112, first paragraph

Claim 1 was rejected under 35 U.S.C. 112, first paragraph, as lacking adequate written description for a negative limitation. This rejection has been withdrawn—see the Advisory Action and Examiner's Answer.

Rejection—35 U.S.C. §112, second paragraph

Claims 11 and 19 were rejected under 35 U.S.C. 112, second paragraph, as being indefinite for using the term "block polymerization". This rejection has been withdrawn—see the Advisory Action and Examiner's Answer.

Rejection—35 U.S.C. §103

Claims 1-12 and 19-20 stand rejected under 35 U.S.C. 103(a) as being obvious over, Haddleton et al., U.S. Patent 5,804,632, in view of Rehmer et al., U.S. Patent No. 6,225,401. The Applicants respectfully request that this rejection be reversed.

> To establish a *prima facie* case of obviousness, three **basic** criteria must be met. First there must be some **suggestion or motivation**, either in the references themselves or in the knowledge generally available to one or ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must **be a reasonable expectation of success**. Finally, the prior art reference (or references when combined) must teach or suggest **all the claim limitations**. (M.P.E.P. 2143) (emphasis added).

Independent Claim 1 requires that the claimed pH-sensitive polymers have particular properties including non-toxicity (i.e., "less than 5% haemolysis at pH 7.4") and membranolytic properties at pH 5.5 (i.e., "at least 60% haemolysis at pH 5.5"). The pH-sensitive polymers of the invention are required to lack transition metal complexes, since these complexes are toxic to cells.

Haddleton was cited as generally disclosing preparing a low molecular weight polymer by free-radical polymerization using a transition metal complex, see e.g., Abstract and col. 5, lines 26-31. Haddleton is not particular about the monomer system used and col. 5, line 26 indicates that "any olefinically unsaturated monomer(s) which is amenable to (co)polymerization using CCT ("catalytic chain transfer") polymerization" can be used. Col. 6, lines 17 *ff.* refer to a range of 1-60 wt% acid comonomers and 99-40% non acid functional comonomers. If methacrylic acid is an acid comonomer, and if alkyl esters of (meth)acrylic acid are non acid functional comonomers, these ranges would appear to overlap the monomer content ranges of Claim 1. Methacrylate is mentioned in col. 6, line 26 as being a useful acid function monomer and non acid functional comonomers like n-butyl methacrylate and

n-butyl acrylate are mentioned on line 33 of col. 6. The Tables in cols. 13 and 14 describe mixtures of methyl methacrylate and methacrylic acid.

The Office has not shown that the Haddleton examples meet the content limitations of Claim 1. However, assuming *arguendo* that Haddleton discloses monomer mixtures of 20-65% by weight methacrylic acid + 80-35% by weight C_1-C_{18}-alkyl esters of (meth)acrylic acid as required by Claim 1, it does not disclose or suggest a mixture (A) lacking transition metal complexes or (B) having the properties required by Claim 1, that is, polymers that bring about at least 60% haemolysis of human red blood cells at pH 5.5, but less than 5% heamolysis at pH 7.4.

Rehmer is cited as disclosing a process for producing copolymers of acrylic and/or (meth)acrylic acid by emulsion polymerization instead of by CCT process used by Haddleton. The obviousness rejection is based on substituting the emulsion polymerization method of Rehmer for the CCT process of Haddleton for the purpose of obtaining the polymers of the invention which do not contain transition metal complexes and which have the pH-sensitive properties required by Claim 1. However, Haddleton and Rehmer even in combination do not suggest the invention for the following reasons.

(A) No motivation for omitting transition metal complexes. There is no motivation in Haddleton for omitting the transition metal complex, since this complex is required to control the molecular weight of the Haddleton polymers. The Haddleton polymers contain toxic transition metal ions, such as cobalt, which remain from a catalytic chain transfer (CCT) polymerization requiring the presence of these toxic metals, see Haddleton, col. 1, lines 50-52 and col. 3, lines 34-40. These remaining transition metals are toxic and would kill cells exposed to them. Similarly, while Rehmer refers to emulsion polymerization, it too does not suggest omission of toxic transition metals. In fact, col. 3, line 23, refers to a process taking place in the presence of "polyvalent metal ions" such as iron and vanadium, thus teaching

away from Claim 1 which requires the absence of transition metals. It is not surprising that Haddleton and Rehmer do not suggest omitting transition metal ions, because they have no reason to specifically exclude toxic metals, since the contemplated polymers are not disclosed for use in biological systems where the lack of transition metal toxicity would be required. Thus, Haddleton and Rehmer do not suggest omitting transition metal complexes.

(B) No motivation for selecting polymers which bring about at least 60% haemolysis at pH 5.5 and less than 5% haemolysis of human red blood cells at pH 7.4.

Page 5, last six lines of the final Official Action indicates that neither Haddleton or Rehmer disclose pH sensitive polymers that bring about at least 60% haemolysis at pH 5.5 and less than 5% haemolysis of human red blood cells at pH 7.4. However, the Official Action indicates that these properties are assumed to be inherent to the polymers of Haddleton and Rehmer, see lines 5-7 on page 6 of the final Official Action. The Official Action is not referring to a polymer exemplified by either Haddleton or Rehmer, but rather the class of polypeptides which could be made using the Rehmer emulsion polymerization process and the ingredients described by Haddleton.

If it is the Official position that all polymers produced using the monomers of Haddleton and the emulsion polymerization process of Rehmer would inherently have the properties required by Claim 1, then this position is clearly rebutted by the experimental data or record. Polymer S-100 (see Tables 1 and 2, pages 25 and 27 of the specification) which falls does NOT have these properties even though it is composed of methacrylic acid and methyl methacrylate monomers.

If all of the polymers the Official Action is referring to do not have the properties required by Claim 1, then this element of the invention is not inherent to the prior art (nor as discussed below is it suggested by either Haddleton or Rehmer).

> To assert that a prior art reference inherently discloses an element of a claimed invention that Office must establish "that missing characteristic is

> necessarily present, or inherent, in the **single anticipating reference**", Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 1268, 20 USPQ2d 1746 (Fed. Cir. 1991)(emphasis added).

Here, the final Official Action cannot establish that the pH-sensitivity limitations in Claim 1 are inherent to the class of prior art polymers because Polymer S-100 is a member of that class and does not have those properties. Moreover, the Office has not pointed out any exemplified polymer in either prior art reference that has these properties.

Haddleton and Rehmer fail to suggest the pH-sensitive polymers of the invention which bring about at least 60% haemolysis of human red blood cells at pH 5.5, but less than 5% heamolysis at pH 7.4. While page 7, line 4 of the final Official Action mentions the term "result effective variable" it does not indicate that the pH-sensitive properties required by the polymers of the invention are results-effective variables. It cannot, since pharmacological use of the Haddleton and Rehmer polymers is not contemplated. Thus, the argument with regard to optimizing a results effective is immaterial to the pH-sensitivity limitations in Claim 1.

Similarly, the prior art provides no reasonable expectation of success for polymers conforming to these limitations, since it does not contemplate the specific pharmacological uses for the pH-sensitive polymers of the invention, e.g., to introduce pharmacological or biological agents into a cell.

Accordingly, since the prior art does not suggest the invention by (A) omitting toxic transition metal complexes and (B) selecting polymers that bring about at least 60% haemolysis of human red blood cells at pH 5.5, but less than 5% heamolysis at pH 7.4, nor provide any reasonable expectation of success for such polymers, the Applicants respectfully request that this rejection be withdrawn.

Arguments in Reply Brief

The Applicants respectfully request consideration of, and response to, their arguments made in their Reply Brief as they pertain to the present claims (which are narrower than the claims previously on appeal). These arguments are reiterated below for the convenience of the Examiner.

Response to Arguments in Examiner's Answer

1. Anticipation and Obviousness. The remaining rejection is an obviousness rejection based on Haddleton, who discloses preparing polymer emulsions for various applications by a method (free-radical polymerization using transition metal catalyst complexes) which introduces transition metals into the resulting polymers; in view of Rehmer, who teaches making copolymers for pressure sensitive adhesives using an emulsion polymerization method which also contemplates use of polyvalent metal ions as well as other types of reducing agents (col. 3, lines 23-24). Neither document suggests making a pH-sensitive polymer that does not contain transition metal complexes and that is substantially non-toxic (i.e., less than 5% haemolysis of red blood cells at pH 7.4). While numerous different types of polymers may be produced for various applications—some toxic, some non-toxic, some pH-sensitive, some pH-insensitive--neither document provides a reasonable expectation of success for producing a pH-sensitive polymer having particular biological properties required by independent claim 1.

2. Citing In re Boesch and Sianey, 205 USPQ 215 (CCPA 1980), the Examiner asserts that it would have been obvious to optimize the prior art copolymer formulations. However, the Examiner's Answer does not indicate which property of the prior art polymers should be optimized or point out where the prior art says that these properties should be optimized

Assuming, *arguendo*, that the prior art suggested the desirability of producing polymers that are non-toxic (i.e., no transition metal complexes) in biological applications, it provides no guidance as to how to optimize these properties, nor does it suggest that reducing transition metal complex content would optimize the non-toxic biological properties of such copolymers. Similarly, there is no suggestion to optimize the chemical formulation of a copolymer to obtain the specific biological properties required by claim 1 ("brings about at least 60% haemolysis at pH 5.5, and less than 5% haemolysis a pH 7.4"). "A particular parameter must be recognized as a results-effective variable. . .before the determination of an optimum or workable ranges of said variable might be characterized as routine experimentation", *In re Antonie*, 195 USPQ 6 (CCPA 1977); MPEP 2144.05(II)(B). Here the Examiner has not shown that minimizing transition metal content of a copolymer was a recognized results-effective variable for producing the claimed pH-sensitive polymer.

3. Page 9, last paragraph, of the Examiner's Answer properly identifies claim 1 as a product claim, but asserts that any process limitations are not material. The claimed pH-sensitive polymer of claim 1 is deemed to be substantially the same as that of Haddleton and Rehmer. Initially, there are no process limitations in claim 1. Claim 1 requires a pH-sensitive polymer that does not contain transition metal complexes. Haddleton teaches a method which would produce aqueous polymers containing transition metal complexes. While Rehmer contemplates polymers produced using emulsion polymerization which may also include transition metals, it does not suggest producing the pH-sensitive polymers of claim 1, nor specifically suggest omitting transition metals. Rehmer is unconcerned with whether a polymer has the properties required by claim 1, because it is directed to making adhesives. Haddleton also is silent about polymers having the functional properties required by claim 1.

4. Page 10, first paragraph, of the Examiner's Answer considers that "the focal argument resides in the contention that there is no motivation for selecting polymers which brings about at least 60% haemolysis at pH 5.5 and less than 5% haemolysis of human red blood cells at pH 7.4". *In re Spada*, 15 USPQ2d 1965 (Fed. Cir. 1990) is cited as indicating that products which are not novel are not rendered novel by recitation of their inherent properties.

As noted by the Examiner's Answer, the rejection on appeal is an obviousness rejection, not an anticipation (lack of novelty) rejection. *In re Spada* concerns an anticipation rejection and the functional properties required by claim 1 are not inherent to the transition metal complex free polymers allegedly suggested by the prior art.

With regard to the issue of obviousness, the prior art provides no suggestion or expectation of success for obtaining a transition metal complex free polymer having the functional properties required by claim 1. These properties are not inherent to polymers produced by the prior art methods as demonstrated by the Applicants. Some polymers, such as that of Polymer S-100 (see page 12, line 7 of the Supplemental Appeal Brief), do not have this functional property. There is no suggestion in the prior art to produce polymers having these properties, or even that polymers having these functional properties can be produced using the prior art methods. This limitation must be addressed for purposes of obviousness, since not all the polymers produced by using emulsion polymerization of Rehmer in conjunction with the process of Haddleton would inherently have these properties; MPEP 2143.03.

In re Best, 195 USPQ 430 (CCPA 1977) is cited to assert that the Applicants must prove that the prior art polymers have different properties than what is claimed. *In re Best* is directed to an anticipation rejection where a functional limitation is critical for establishing novelty of a product and indicates:

> Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require the Applicant to prove that the prior art products **do not necessarily or inherently possess the characteristics of his claimed product**.

The Applicants have shown that the genus of polymers that could be produced by the combination of prior art methods does **not necessarily or inherently possess the characteristics** of the polymer of claim 1. Not all polymers produced by prior art methods have these properties as evidenced by Polymer S-100. Moreover, the prior art provides no motivation for producing the pH-sensitive polymers having the functional properties required by claim 1 both with regard to (i) omitting toxic transition metal complexes and with respect to (ii) the specific pH-sensitive properties required by the last clause in claim 1.

New Information Disclosure Statement

The following documents are cited on the attached information disclosure statement and were cited on a Japanese Examination Reported dated September 12, 2007.

JP 09-501457 ("JP-D1") corresponds to Haddleton, et al., U.S. Patent No. 5,804,632 cited in the rejection above.

JP 02-242807 ("JP-D2") no U.S. equivalent. English translation attached. This publication is n0on-analogous art in that it does not pertain to pharmaceutical preparations. The polymers exemplified by Example 1 and Comparative Example 1 fall outside the present claim language.

JP 08-081392 ("JP-D3") corresponds to U.S. Patent 5,644,011.

CONCLUSION

In view of the above amendments and remarks, the Applicants respectfully submit that this application is now in condition for allowance. An early notification to that effect is earnestly solicited.

Respectfully submitted,

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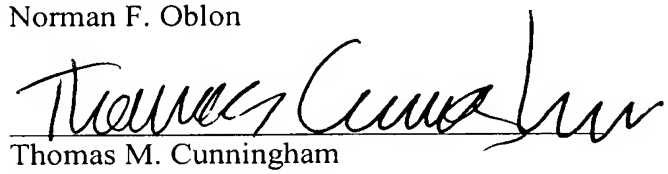

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